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6. AUTHOR(S)
PAUL N. AUSTIN

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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This is to certify that Paul N. Austin in the Graduate Program, School of Nursing, has successfully completed his research project entitled, **THE COMBINATION OF ATRACURIUM AND VECURONIUM COMPARED TO VECURONIUM ADMINISTERED ALONE: EVALUATION OF THE TIME OF ONSET, DURATION OF ACTION, INTUBATING CONDITIONS AND CARDIOVASCULAR EFFECTS** in partial fulfillment of the requirements for the degree of Master of Science.

Signatures:

Nadine Fallacaro CRNA MS 4-20-90

Nadine Fallacaro CRNA MS Clinical Instructor

Committee Chairperson date

4-20-90

Roger E. Kaiser Jr MD Assistant Clinical Professor

Committee Member date

Date: June 1990

ABSTRACT

Succinylcholine is often used as the neuromuscular relaxant to facilitate endotracheal intubation in the patient presenting for emergency surgery. However, it is contraindicated in some patient subgroups.

The purpose of this double blind, randomized study was to investigate the use of the combination of atracurium and vecuronium compared to vecuronium used alone for accomplishing skeletal muscle relaxation to facilitate endotracheal intubation. This study was designed to test the hypotheses that the combination of atracurium 0.40 mg/kg plus vecuronium 0.10 mg/kg (combination group) will result in a significantly shorter onset time and duration of action and will produce better intubating conditions with no differences in cardiovascular effects compared to vecuronium 0.28 mg/kg (vecuronium group) administered alone intravenously.

Forty A.S.A. physical status I or II adult patients who were otherwise healthy and scheduled to undergo non-hepatic, non-renal surgical procedures of at least 2 hours duration were randomly assigned to receive either the combination of atracurium and vecuronium or vecuronium alone. The anesthetic technique was standardized using a nitrous oxide, narcotic, barbiturate technique. Neuromuscular function was measured and recorded using the mechanical force potential of the thumb in response to stimulation of the ulnar nerve

at the wrist.

Data was analyzed with the chi-square statistic, Student's t-test, and Bonferroni t-tests. A significance level of < 0.05 was used to reject the null hypothesis. The two groups were homogenous in regards to age and weight, however, the vecuronium group was comprised of a disproportionately large number of males.

There were no significant differences in the onset (95% twitch height reduction) times (142 seconds for the combination group, 134 seconds for the vecuronium group), intubating conditions, and cardiovascular effects (heart rate and blood pressure) between the two groups. The duration of action (25% twitch height recovery) of the combination of atracurium and vecuronium, 69.7 minutes, was significantly shorter than when the vecuronium was administered alone, 83.8 minutes.

Future studies may confirm that the combination of atracurium and vecuronium is preferable to vecuronium administered alone for facilitation of endotracheal intubation when succinylcholine is contraindicated.

THE COMBINATION OF ATRACURIUM AND VECURONIUM COMPARED TO VECURONIUM ADMINISTERED ALONE: EVALUATION OF THE TIME OF ONSET, DURATION OF ACTION, INTUBATING CONDITIONS, AND CARDIOVASCULAR EFFECTS.

by

Paul N. Austin

A project submitted to the Faculty of the Graduate School of the State University of New York at Buffalo in partial fulfillment of the requirements for the degree of Master of Science

June 1990

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INTRODUCTION

Succinylcholine is often used as the neuromuscular relaxant to facilitate endotracheal intubation in the patient presenting for emergency surgery (1). However, due to its side effects, it is contraindicated in some patient subgroups (2-8).

This has lead to the use of non-depolarizing neuromuscular relaxants in these situations. Methods used to decrease their onset time include using large doses (9), using a "priming dose" (10,11), and combining two non-depolarizing neuromuscular relaxants (12-15).

The purpose of this study was to investigate the use of the combination of atracurium and vecuronium compared to vecuronium used alone for accomplishing skeletal muscle relaxation to facilitate endotracheal intubation. This study was designed to test the hypotheses that the combination of atracurium 0.40 mg/kg plus vecuronium 0.10 mg/kg (combination group) administered intravenously will result in a shorter onset time and duration of action and will produce better intubating conditions compared to vecuronium 0.28 mg/kg (vecuronium group) administered alone intravenously. In addition, the hypothesis that the combination will produce no different cardiovascular effects compared to vecuronium administered alone was tested.

MATERIAL AND METHODS

The study was approved by the State University of New York at Buffalo School Nursing Human Subjects Review Board. The State University of New York at Buffalo School of Medicine and Biomedical Sciences Institutional Review Board gave approval for the study to be conducted at the Erie County Medical Center. Written informed consent was obtained from all patients.

Forty American Society of Anesthesiologists physical status I or II adult patients of either gender were randomly assigned to receive the combination of atracurium plus vecuronium or vecuronium alone. Criteria for entry included absence of renal, hepatic, and neuromuscular diseases. Patients were scheduled to undergo non-renal, non-hepatic surgical procedures of at least 2 hours duration requiring neuromuscular relaxation. Patients were excluded from the study if they were receiving medications known to affect neuromuscular function. The study was conducted in a double blind fashion.

Intravenous access was established pre-operatively and 0.2mg of glycopyrrolate, the only pre-medicant, was administered IV. Monitors included EKG, precordial stethoscope, automated blood pressure monitor, end-tidal carbon dioxide, oxygen saturation, and esophageal temperature. During pre-oxygenation, fentanyl 1.5 mcg/kg was administered IV. Anesthesia was then induced with

thiamylal 3-7 mg/kg IV and ventilation was controlled as necessary to maintain normal end-tidal carbon dioxide concentrations. After recording baseline neuromuscular function, heart rate, and blood pressure; either atracurium 0.40 mg/kg and vecuronium 0.10 mg/kg (in separate syringes) or vecuronium 0.28 mg/kg was administered as a bolus via a proximal port into a rapidly flowing IV. The trachea was intubated orally under direct vision when 95% twitch height depression occurred. Anesthesia was maintained with 60-70% nitrous oxide in oxygen. During the first 10 minutes after administration of the relaxant(s), when recordings of heart rate and blood pressure were obtained, only thiamylal 50 to 100 mg was administered IV if it was felt necessary to supplement the nitrous oxide. After this 10 minute period, intermittent doses of fentanyl or sufentanil with thiamylal and/or midazolam were administered IV to supplement the nitrous oxide. End-tidal carbon dioxide concentration was maintained within the normal range using mechanical ventilation. Esophageal temperature was maintained between 35 to 37 degrees C. The study was concluded when twitch height returned to 25% of control and the remainder of the anesthetic was conducted as deemed appropriate by the anesthesia team.

The ulnar nerve was supramaximally stimulated at the wrist using surface electrodes. Frequency of stimulation was 0.1 Hz using square wave impulses of 0.2 milliseconds in

duration supplied by a Digistim II peripheral nerve stimulator (Neuro Technology, Houston, TX). Evoked force of thumb potential was measured with a Grass FT-10 force-displacement transducer and recorded with a Grass Model 5 polygraph (Grass Instrument Company, Quincy, MA.).

Times to 95% twitch height depression (onset time) and to 25% twitch height recovery (duration of action) were recorded. Heart rate, systolic, diastolic, and mean blood pressures were recorded prior to administration of the relaxant(s) (baseline) and 2, 5, and 10 minutes after relaxant(s) administration. The laryngoscopist graded the intubation conditions using the scale described in table 1 (16).

Group homogeneity was assessed in regards to age and weight using Student's t-test and in regards to gender with Chi-square analysis. The mean times to 95% twitch height depression and to 25% recovery were compared between the two groups using Student's t-test. Endotracheal intubation conditions were compared between the two groups using Chi-square analysis. Mean heart rate and systolic, diastolic, and mean blood pressures at 2, 5, and 10 minutes after administration of the relaxant(s) were compared between the two groups using Bonferroni t-tests. Computer analysis of the data was performed with the Statistical Package for the Social Sciences-X. (SPSS Inc., Chicago, IL.) A significance level of < 0.05 was used to reject the null hypothesis.

Table 1. Endotracheal Intubation Conditions

1 Point: Excellent. Jaw and vocal cords well relaxed, no cough or movement upon laryngoscopy and/or intubation.

2 Points: Good. Jaw and vocal cords well relaxed, slight cough upon laryngoscopy and/or intubation.

3 Points: Poor. Jaw not well relaxed, vocal cords slightly adducted, cough or movement upon laryngoscopy and/or intubation.

4 Points: Impossible. Jaw and/or vocal cords tightly closed.

RESULTS

The groups were similar except in respect to gender, as shown in table 2. The vecuronium group was composed mainly of males, while the combination group had a more even distribution of males and females.

Onset times between the two groups were not different (Table 3). However, the duration of action of the combination group was shorter compared to the vecuronium group (Table 4). The duration of action was not obtained in 2 patients in the vecuronium and in 1 patient in the combination group because the surgical procedures concluded prior to the twitch height returning to 25% of control.

Intubation conditions were excellent in all patients except for 1 patient in the vecuronium group (Table 5). This patient coughed slightly upon intubation.

There were no differences between the two groups in regard to heart rate and systolic, diastolic, and mean blood pressures when measured at baseline and 2, 5, or 10 minutes after the relaxant(s) was administered (Tables 6 - 9).

Table 2. Summary of Demographics and Physical Characteristics of All Patients

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=20)	Vecuronium 0.28 mg/kg (n=20)
Age (yrs)	31 ± 1.8(a)	36 ± 3.2
Weight (kg)	77.0 ± 3.9(a)	80.9 ± 3.0
Gender (actual number)		
Male	11(b)	18
Female	9	2

a. Mean ± S.E.M.

b. The groups were not homogeneous in regards to gender ($p<0.05$)

Table 3. Onset of Neuromuscular Blockade

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=20)	Vecuronium 0.28 mg/kg (n=20)
Time from injection to 95% twitch height depression (seconds)	142 ± 11.2(a)	134 ± 8.2

a. Mean ± S.E.M.

No significant differences detected between the groups.

Table 4. Duration of Action

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=19)	Vecuronium 0.28 mg/kg (n=18)
Time from injection to 25% twitch height recovery (minutes)	69.7 ± 3.9(a)	83.8 ± 6.6(b)

Note: The duration of action was not obtained in 1 patient in combination group and 2 patients in vecuronium group due to the surgical procedures concluding prior to the twitch height returning to 25% of control.

a. Mean ± S.E.M.

b. Significantly different from combination group ($p<0.05$).

Table 5. Intubating Conditions at 95% Twitch Height Depression

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=20)	Vecuronium 0.28 mg/kg (n=20)
Excellent	20(a)	19
Good	0	1
Poor	0	
Impossible	0	0

a. Actual number of patients.

No significant differences detected between the groups.

Table 6. Heart Rate

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=20)	Vecuronium 0.28 mg/kg (n=20)
Baseline(a)	81 ± 3.5	73 ± 3.5
2 min(b)	92 ± 4.2	84 ± 5.1
5 min	96 ± 4.4	91 ± 4.6
10 min	83 ± 4.0	88 ± 4.4

a. Beats per minute, Mean ± S.E.M.

b. 2, 5, and 10 minutes after injection.

No significant differences detected between the groups.

Table 7. Systolic Blood Pressure

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=20)	Vecuronium 0.28 mg/kg (n=20)
Baseline(a)	129 ± 2.9	132 ± 3.2
2 min(b)	127 ± 5.7	122 ± 4.1
5 min	137 ± 4.6	130 ± 4.5
10 min	122 ± 5.0	126 ± 3.6

a. Torr, Mean ± S.E.M.

b. 2, 5, and 10 minutes after injection.

No significant differences detected between the groups.

Table 8. Diastolic Blood Pressure

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=20)	Vecuronium 0.28 mg/kg (n=20)
Baseline(a)	72 ± 2.4	72 ± 3.2
2 min(b)	73 ± 3.9	69 ± 4.7
5 min	82 ± 4.3	76 ± 3.7
10 min	72 ± 3.9	74 ± 3.1

a. Torr, Mean ± S.E.M.

b. 2, 5, and 10 minutes after injection.

No significant differences detected between the groups.

Table 9. Mean Blood Pressure

	Group	
	Atracurium 0.40 mg/kg + Vecuronium 0.10 mg/kg (n=20)	Vecuronium 0.28 mg/kg (n=20)
Baseline(a)	91 ± 2.3	92 ± 3.0
2 min(b)	92 ± 4.1	85 ± 4.4
5 min	102 ± 3.9	95 ± 3.9
10 min	91 ± 3.9	89 ± 2.9

a. Torr, Mean ± S.E.M.

b. 2, 5, and 10 minutes after injection.

No significant differences detected between the groups.

DISCUSSION

With the introduction of the intermediate acting non-depolarizing neuromuscular relaxants, atracurium and vecuronium, it was thought they would offer an alternative to succinylcholine as the neuromuscular relaxant used to facilitate endotracheal intubation during rapid sequence inductions. However, their use in this setting has several drawbacks. It was found that large doses of atracurium (17) and vecuronium (18) were needed to provide an acceptable onset time. While not of the magnitude of the long acting non-depolarizing neuromuscular relaxants, the duration of both is prolonged as the dose is increased (19,20). In addition, with doses of atracurium that are needed for rapid sequence induction, a reduction in systemic vascular resistance and blood pressure may be seen (21). Studies have demonstrated vecuronium is essentially devoid of cardiovascular side effects in most instances (21). Bradycardia and hypotension have been reported when vecuronium has been administered simultaneously with large doses of narcotics, such as in patients undergoing open-heart surgery (22).

In the search for methods to decrease the onset time of the non-depolarizing neuromuscular relaxants, studies have been reported using the "priming principle" (10,11). While this technique has been shown to decrease onset time, disadvantages include the need to use 3 times the amount of

neuromuscular relaxant needed to produce 95% twitch height depression (3 X ED95) with the accompanying prolongation of the duration of action. The other chief disadvantage is having to administer the "priming dose" when the patient is awake. Reported side effects of this technique include the patient experiencing the unpleasant sensation of being weak (23), difficulty swallowing (24), and pulmonary aspiration (25).

Another method that has been investigated to decrease the onset time of non-depolarizing neuromuscular relaxants is combining two non-depolarizing neuromuscular relaxants. In the early 1980's, Lebowitz et al. reported findings which supported the hypothesis that there exists a synergism between pancuronium and curare and pancuronium and metocurine (12,13). This synergism is reported to be due to the pre-junctional effects of curare and metocurine and the post-junctional effects of pancuronium. Use of the combination does shorten the onset time and reduces the incidence of cardiovascular side effects compared to when the neuromuscular relaxants are used alone. However, the duration of action of the combination remains long.

As a result of the work done by Lebowitz et al., Berman et al. compared the onset time and duration of action of atracurium, 0.50 mg/kg (about 2.5 X ED95) and vecuronium, 0.10 mg/kg (approximately 2 X ED95) and three combinations of atracurium and vecuronium (14). Like metocurine,

atracurium is molecularly similar to curare and vecuronium is similar to pancuronium. It was felt there may be a synergism between atracurium and vecuronium as there is between metocurine and pancuronium and curare and pancuronium. Of the three combinations studied (50%, 70%, 80% each of the control doses of atracurium and vecuronium), the third combination of 80% each of the control doses (atracurium 0.40 mg/kg and vecuronium 0.08 mg/kg) resulted in the fastest time to 90% twitch height depression (86.8 seconds). The time to 25% twitch height recovery (60 minutes) was only 10 minutes longer than the combination of 50% of each of the control doses of atracurium and vecuronium. They did not quantitatively report intubating conditions. Their sample consisted of 50 patients, 10 patients per group.

Silverman et al. also investigated use of the combination of atracurium and vecuronium (15). They compared succinylcholine and vecuronium administered alone and vecuronium administered in combination with atracurium. The twitch height at 90 seconds and time to 95% twitch height depression were compared. This study differed from that of Berman et al.(14) in that different doses of atracurium and vecuronium were used. Also priming doses of atracurium and vecuronium utilized. Using a priming dose of 0.05 mg/kg of atracurium and the combination of vecuronium 0.06 mg/kg and atracurium 0.40 mg/kg, the mean time to 95%

twitch height depression was 119.5 seconds. Keeping all other doses constant and raising the dose of vecuronium to 0.18 mg/kg produced a mean time to 95% twitch height depression of 126.0 seconds. They did not report the duration of action or intubating conditions. Their sample consisted of 75 patients, 6 - 8 patients per group.

The findings from these studies were supported by work done by Van Der Spek et al. (26). They used an in vitro rat phrenic nerve-hemidiaphragm preparation to study the synergism between vecuronium and atracurium. They concluded there is a synergism between these two drugs in vitro which is probably due to multiple receptor sites and different modes of action of the competitive neuromuscular blocking agents.

The doses we chose for the combination of atracurium and vecuronium were based on the findings of Berman et al. (14). We chose the doses which decreased the onset time the most while producing minimal prolongation of action. We chose 0.28 mg/kg of vecuronium to compare the combination to because at this dose it has a relatively rapid onset, intermediate duration of action, and lacks cardiovascular side effects. We felt it is probably preferred by clinicians for facilitation of endotracheal intubation during rapid sequence induction when succinylcholine is contraindicated.

It is not clear why there were differences between the

two groups in regards to gender. A possible explanation is that during the period of time the study was conducted, more males than females presented for surgery. Alternatively, there were fewer patients presenting for gynecological surgery during the study period.

The onset time in the vecuronium group (134 seconds or 2.2 minutes) was similar to the onset time found by Fahey et al. (2.1 minutes) (19). However, we defined onset time as time to 95% twitch height depression and they used time to maximal twitch height depression. Also, there are differences in sample size, 8 patients in this group in their study compared to 20 patients per group in our study. Lennon, Olsen, and Gronert found the time to 95% twitch height depression to be 64 seconds for 0.25 mg/kg of vecuronium (27). However, they not only used a slightly different dose but also used a stimulus frequency of 1 Hz rather than 0.1 Hz. Because the extent of neuromuscular blockade is frequency dependent (28), it is not surprising these investigators found a shorter time of onset using a frequency 10 times greater than we used. Three studies, using 0.30 mg/kg, found the mean time to maximal twitch height depression to be 88 to 130 seconds (29, 30, 31). Compared to our study, these three studies used a higher dose of vecuronium and had only 10 patients per group.

The duration of action in the vecuronium group, defined as 25% twitch height recovery, was 83 minutes. Lennon,

Olsen, and Gronert found the time to return of 2 twitches in the train-of-four to be 83 minutes for 0.25 mg/kg of vecuronium (27). Studies have reported the time to 25% twitch height recovery for 0.30 mg/kg of vecuronium to be 100 to 111 minutes (29, 30, 31). Again, they used a higher dose of vecuronium and had a smaller sample size. Fahey et al., using 0.28 mg/kg, defined duration of action as time to 90% twitch height recovery and found it to be 174 minutes (19).

We found that by administering about 2 X ED95 each of atracurium and vecuronium, the onset time did not differ significantly from approximately 5 X ED95 of vecuronium. This finding did not support our first hypothesis. This may of occurred because we did not use doses of atracurium and vecuronium (2 x ED95 of each) which are equipotent to the dose of vecuronium (about 5 X ED95) we administered alone. Perhaps this could be shown by future studies using equipotent doses of atracurium and vecuronium. While our findings differ from Berman et al. and Silverman et al.(14,15) it should be noted we used as an end point for intubation 95% rather than 90% twitch height depression and we administered slightly different doses of atracurium and vecuronium with no priming dose.

The combination resulted in a significantly shorter duration of action compared to vecuronium administered alone, supporting our second hypothesis. This may be due to

these two neuromuscular relaxants having different routes of metabolism and elimination. Atracurium is metabolized and eliminated by ester hydrolysis and Hoffman elimination (20). It has been reported that 10 - 15% of an injected dose of vecuronium is excreted in the urine with 75 to 80% excreted in the bile (32). With different pathways of elimination, perhaps no one pathway is overwhelmed. Another possible reason the combination resulted in a shorter duration of action is that when smaller doses of vecuronium are administered, such as in the combination group, serum concentration falls rapidly due to redistribution of the drug (32). With larger doses, such as in the group which received 0.28 mg/kg of vecuronium, a decrease in serum concentration is more dependent on metabolism and elimination (32). The duration of action of the combination, 69.7 minutes, was slightly longer than that reported by Berman et al., 60.8 minutes (14). The difference may be due to using different neuromuscular monitoring techniques (evoked mechanical potential as opposed to integrated EMG), slightly different doses, and differences in sample size. Twenty five per cent twitch height recovery was chosen to define duration of action because at that degree of recovery, residual neuromuscular relaxation can readily be reversed in the vast majority of patients (33).

In regards to intubating conditions, we found no

difference in the intubating conditions between the two groups. This did not support our third hypothesis. This finding is not surprising because we intubated the patients in both groups at 95% twitch height depression (34). We chose to intubate at that level of neuromuscular blockade because when intubating certain patients, such as those with an open eye injury who present for an emergent surgical procedure, one would like to be as certain as possible the patient will not cough or buck when intubated. Indeed, adequate intubating conditions may result with as little as 40 to 60% twitch height depression (35). However, the reliability of attaining excellent intubating conditions increases directly with the level of neuromuscular blockade (36). The reason why good intubating conditions are present with less than 95 or 100% neuromuscular blockade measured at the adductor pollicis may be because those muscles which must be blocked for intubation receive more blood flow compared to peripheral muscles, such as the adductor pollicis (27). Other factors may be anesthetic depth at intubation and experience of the laryngoscopist. As an incidental finding, we found 75% twitch height depression at 97 seconds for the vecuronium group and 103 seconds for the combination group. In future studies, it would be useful to compare intubation conditions between these two groups at less than 95% twitch height depression. It is likely one would find adequate intubating conditions about 90 seconds

after relaxant administration.

Our findings regarding cardiovascular effects supported our final hypothesis. The lack of differences in cardiovascular effects between the two groups agrees with other studies which have shown vecuronium to be devoid of cardiovascular effects in most instances and studies which have shown that significant histamine release due to atracurium is unlikely when it is administered in doses less than 0.60 mg/kg (21). No patient in either group exhibited localized signs of histamine release. These cardiovascular effects would perhaps be better studied with an experimental design such as the one used by Morris et al.(37) where there is no painful stimulation (such as endotracheal intubation) during the study period and a pulmonary artery catheter is used so other parameters may be assessed, such as systemic vascular resistance and cardiac output.

SUMMARY AND CONCLUSIONS

In summary, administration of the combination of atracurium 0.40 mg/kg plus vecuronium 0.10 mg/kg resulted in a significantly shorter duration of action than when vecuronium 0.28 mg/kg was administered alone IV. The onset time, intubation conditions, and cardiovascular effects were not significantly different when compared between the two groups.

Our findings suggest that this combination of atracurium and vecuronium may be preferable to vecuronium 0.28 mg/kg used alone to facilitate endotracheal intubation in cases where succinylcholine is contraindicated. These findings should be confirmed with future studies before this technique is incorporated into practice. Future studies should further investigate if there exists a synergism between atracurium and vecuronium. In addition, future studies should investigate if adequate intubating conditions are present with less than 95% twitch height depression.

REFERENCES

1. Gibbs CP, Modell JH: Aspiration pneumonitis. In Miller RD, ed. Anesthesia (2nd ed.). New York: Churchill-Livingstone, 1986:2023-50.
2. Bruce RA, McGoldrick DE, Oppenheimer P: Anesthesia for Ophthalmology. Birmingham:Aesculapius,1982:74-5.
3. Miller RD, Way WL, Hickey RF: Inhibition of succinylcholine-induced intraocular pressure by non-depolarizing muscle relaxants. Anesthesiology 1968;29:123-6.
4. Halldin M, Wahlin A: Effect of succinylcholine on the intraspinal pressure. Acta Anaesthesiol Scand 1959; 3:155-61.
5. Birch AA, Mitchell GD, Playford GA: Changes in serum potassium response to succinylcholine following trauma. JAMA 1969;210:490-3.
6. Cooperman LH: Succinylcholine induced hyperkalemia in neuromuscular disease. JAMA 1971;213:1867-71.
7. Schaner PJ. Brown RL, Kirksey TD, Gunther RC, Ritchey CR, Gronert GA: Succinylcholine induced hyperkalemia in burned patients. Anesthesia and Analgesia 1969;48:764-70.
8. Stevenson PM, Birch AA: Succinylcholine induced hyperkalemia in a patient with a closed head injury. Anesthesiology 1979;51:89-90.

9. Miller RD, Savarese JJ: Pharmacology of muscle relaxants and their antagonists. In Miller RD, ed. Anesthesia (2nd ed.). New York:Churchill-Livingstone, 1986:889-943.

10. Mehta MP, Choi WW, Gergis SD, Sokoll MD, Adolphson AJ: Facilitation of rapid endotracheal intubation with divided doses of non-depolarizing neuromuscular blocking drugs. Anesthesiology 1985;62:392-5.

11. Schwarz S, Ilias W, Lackner F, Maryrhofer 0, Foldes, FF: Rapid endotracheal intubation with vecuronium: The priming principle. Anesthesiology 1985;62:388-91.

12. Lebowitz PW, Ramsey, FM, Saverase JJ, Ali HH: Potentiation of neuromuscular blockade in man produced by combinations of pancuronium and metocurine or pancuronium and d-tubocurarine. Anesthesia and Analgesia 1980;59:604-9.

13. Lebowitz PW, Ramsey RH, Savarese JJ, Ali HH, deBros FM: Combination of pancuronium and metocurine: Neuromuscular and hemodynamic advantages over pancuronium. Anesthesia and Analgesia 1981;60:12-17.

14. Berman JA, Suh KK, Bleiweiss W, Seskin M: Evaluation of atracurium and vecuronium in combination to facilitate endotracheal intubation. Anesthesiology 1985;63:A342.

15. Silverman DG, Swift CA, Hartmann KA, Sinatra RS, Dubow HD: Onset of blockade with vecuronium alone or combined: a reassessment under uniformed controlled conditions. Anesthesiology 1988;69:A881.

16. Young HSA, Clarke RSJ, Dundee JW: Intubating conditions with AH 8165 and suxamethonium. Anaesthesia 1975;30:30.

17. Twohig MM, Ward S, Corall IM: Conditions for tracheal intubation using atracurium compared to pancuronium. Br J of Anaesth 1983;55:87S-89S.

18. Casson WR, Jones RM: Vecuronium induced neuromuscular blockade: The effect of increasing dose on speed of onset. Anaesthesia 1986;41:354-7.

19. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P: Clinical pharmacology of ORG NC45 (Norcuron™): A new non-depolarizing neuromuscular relaxant. Anesthesiology 1981;55:6-11.

20. Basta ST, Ali HH, Savarese JJ, Sunder N, Gionfrido M, Cloutier G, Lineberry C, Cato AE: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscular relaxant. Anesthesia and Analgesia1982; 61:723-9.

21. Hunter JM: Adverse effects of neuromuscular blocking drugs. Br J Anaesth 1987;59:46-60.

22. Gravlee GP, Ramsey FM, Roy RC, Angert KC, Rogers AT, Pauca AL: Rapid administration of a narcotic and neuromuscular blocker: A hemodynamic comparison of fentanyl, sufentanil, pancuronium, and vecuronium. Anesthesia and Analgesia 1988;67:39-47.

23. Sosis M, Stiner A, Larijan GE, Marr AT: An evaluation of priming with vecuronium. Br J of Anaesth 1987; 59:1236-9.

24. Taboada JA, Rupp SM, Miller RD: Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. Anesthesiology1986;64:243-7.

25. Musich J., Walts LF. Pulmonary aspiration after a priming dose of vecuronium. Anesthesiology 1986;64:517-9.

26. Van Der Spek AFL, Zupan JT, Pollard BJ, Schork MA: Interactions of vecuronium and atracurium in an in vitro nerve-muscle preparation. Anesthesia and Analgesia 1988;67:240-6.

27. Lennon RL, Olson RA, Gronert GA. Atracurium or vecuronium for rapid sequence endotracheal intubation. Anesthesiology 1986;64:510-13.

28. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216-49.

29. Ginsberg B, Glass PS, Quill T, Shafron D, Ossey KD. Onset and duration of neuromuscular blockade following high-dose vecuronium administration. Anesthesiology 1989;71:201-5.

30. Kaufman JA, Dubois MY, Chen JC, Lea DE. Pharmacodynamic effects of vecuronium: A dose response study. J. Clin. Anesth. 1989;1:434-9.

31. Tullock WC, Diana P, Cook DR, Wilks DH, Brandom BW, Beach CA. High dose vecuronium: Onset and duration. Anesthesia and Analgesia 1988;67:S266.

32. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ: Clinical pharmacology of vecuronium and atracurium. Anesthesiology 1984;61:444-53.

33. Katz RL: Clinical neuromuscular pharmacology of pancuronium. Anesthesiology 1971;34:550.

34. Donlon JV, Ali HH, Savarese JJ: A new approach to the study of four non-depolarizing relaxants in man. Anesthesia and Analgesia 1974;53:934-9.

35. Agoston S, Salt P, Newton D, Bencini A, Boomsma P, Erdmann W: The neuromuscular blocking action of Org NC 45, a new pancuronium derivative, in anaesthetised patients. A pilot study. Br J of Anaesth 1980;52:53S-59S.

36. Mirakhur RK, Ferres RS, Clarke RSJ, Bali IM, Dundee JW: Clinical evaluation of ORG NC45. Br J of Anaesth 1983;55:119-24.

37. Morris RB, Cahalan MK, Miller RD, Wilkinson PL, Quash Al, Robinson SL. The cardiovascular effects of vecuronium (ORG NC45) and pancuronium. Anesthesiology 1983;53:438-40.

APPENDIX A
SUNY at Buffalo School of Nursing
Human Subjects Review Committee Approval

UNIVERSITY AT BUFFALO
STATE UNIVERSITY OF NEW YORK

School of Nursing
1105 Stockton Kimball Tower
Buffalo, New York 14214
(716) 831-2510

May 24, 1989

Paul N. Austin, CRNA
401 Guilford Lane
Williamsville, NY 14221

Dear Mr. Austin:

Your proposal entitled "Vecuronium compared to the combination of atracurium and vecuronium: evaluation of the time of onset, duration of action, quality of relaxation and cardiovascular effects" has been reviewed and approved for 12 months with the understanding that it is going to be done under the direct supervision of Dr. Roger E. Kaiser.

Please inform the Human Subjects Review Committee if any eventuality should arise with your research which raises additional issues with respect to risks to the subjects and/or confidentiality of the data.

Sincerely,

Gail P. Brown

Gail P. Brown, R.N., Ph.D.
Chairperson
Human Subjects Review Committee

GPB:mb
Attachment
cc: Nadine Fallacaro, M.S.

APPENDIX B
SUNY at Buffalo School of Medicine and Biomedical Sciences
Institutional Review Board Approval

UNIVERSITY AT BUFFALO
STATE UNIVERSITY OF NEW YORK

Department of Medicine
School of Medicine
Faculty of Health Sciences
Erie County Medical Center
462 Grider Street
Buffalo, New York 14215
(716) 898-3000

May 19, 1989

Roger E. Kaiser, Jr., M.D.
Department of Anesthesiology
Erie County Medical Center
462 Grider Street
Buffalo, New York 14215

Dear Dr. Kaiser:

The proposal "Effects of vecuronium compared to the combination of atracurium and vecuronium" was unanimously approved by the SUNY School of Medicine and Biomedical Sciences Institutional Review Board pending the following:

1. Addition to the consent form of any specific risks resulting from administration of the combined muscle relaxants.

2. Omit "rare" from last paragraph, 1st page of the consent form.

As soon as we receive the amended material, the proposal will be processed through the research office.

Sincerely yours,

James B. Lee, M.D.
Professor of Medicine
IRB Chair

JBL/al

APPENDIX C

CONSENT FORM

I, the undersigned, agree to participate in this research study. The study is sponsored by the State University of New York at Buffalo School of Nursing and the Department of Anesthesiology of the Erie County Medical Center.

The purpose of this study is to investigate the differences in onset, duration, quality of muscle relaxation and effects on the heart rate and blood pressure of two drugs which are routinely used to produce muscle relaxation during general anesthesia, atracurium and vecuronium. In the study, either vecuronium will be administered alone or the combination of atracurium and vecuronium will be administered. Both of the drugs will be used in accordance with FDA approved guidelines. The effects of the drugs will be evaluated with a peripheral nerve stimulator and by recording of your vital signs, both of which are the standard of care during all general anesthetics. Other aspects of your anesthesia will be conducted in the routine fashion. The surgical procedure which you are scheduled to undergo routinely requires muscle relaxation.

Possible complications of these muscle relaxants include an allergic reaction, skin rash, wheezing, increase or decrease in blood pressure, and increase in heart rate; and if they occur will be treated in the standard fashion. There are no specific risks which result from the administration of the combination of atracurium and vecuronium. There is a potential for weakness after you have emerged from the general anesthesia that may require the breathing tube to be temporarily left in your windpipe and your breathing be assisted by a machine.

Participation in this study is voluntary and refusal will not alter your care. You may not benefit directly from this study. The information gained, however, may aid in the anesthetic care of other patients.

You may withdraw yourself from this study at any time without penalty. Although your records may be inspected by the sponsor and the FDA, you will not be identified by name but only by code number.

The Erie County Medical Center has no specific reimbursement in case of injury.

I acknowledge that I have had the above explained to me and have been given the opportunity to have questions concerning this study answered.

I acknowledge having received a copy of this consent form.

(Patient) (Patient's name)

(Witness)

If any questions arise, your professional contacts are listed below.

Paul N. Austin, CRNA (Investigator) Professional Contact	898-3549
Roger Kaiser, MD (Investigator) Professional Contact	898-3549
Nadine Fallacaro, CRNA (Investigator) Professional Contact	898-3549

APPENDIX D

DATA COLLECTION FORM

ATRACURIUM-VECURONIUM STUDY

DATE: __ __ / __ __ (Mon/day) INTUBATOR __ __
1 2 3 4 5 6

SUBJECT NUMBER: __ __ "A" NUMBER: __ __ __ __ __ __
7 8 9 10 11 12 13 14

GROUP: __ (Vec=1, Atra + Vec=2)
15

AGE: __ __ SEX: __ (Female=1, Male=2)
16 17 18

WEIGHT: __ __ __ (In kg)
19 20 21

BASELINE

HR: __ __ __ SYS: __ __ __ DIA: __ __ __ MAP: __ __ __
22 23 24 25 26 27 28 29 30 31 32 33

ONSET: __ __:__ __ (Minutes:seconds)

__ __ __ (Seconds)
34 35 36

INTUBATING CONDITIONS: __
37

2 MINUTES POST INJECTION

HR: __ __ __ SYS: __ __ __ DIA: __ __ __ MAP: __ __ __
38 39 40 41 42 43 44 45 46 47 48 49

5 MINUTES POST INJECTION

HR: __ __ __ SYS: __ __ __ DIA: __ __ __ MAP: __ __ __
50 51 52 53 54 55 56 57 58 59 60 61

10 MINUTES POST INJECTION

HR: __ __ __ SYS: __ __ __ DIA: __ __ __ MAP: __ __ __
62 63 64 65 66 67 68 69 70 1 2 3

DURATION: __ __ __:__ __ (Minutes:seconds)

__ __ __ __ __
4 5 6 7 8

INTUBATOR CODE

Austin: 1	Adragna: 11	Mendez: 21	Smith: 31
Fallacaro: 2	Delaney: 12	Schmidt: 22	Tamirisa: 32
Fino: 3	Kaiser: 13	Kuneru: 23	Motamed: 33
Hasset: 4	Maceda: 14	Peters: 24	Sperarrza: 34
Radel: 5	Nesarajah: 15	Murdock: 25	
Schrader: 6	Nohjel: 16	Sumner: 26	
Schwanekamp: 7	Schuder: 17	Polchetti: 27	
Troy: 8	Venditti: 18	Chaney: 28	
White: 9	Vogt: 19	Sievenpiper: 29	
Zukic: 10	Stanton: 20	Northern: 30	

INTUBATING CONDITIONS

1 Point: Excellent. Jaw and vocal cords well relaxed, no cough or movement upon laryngoscopy and/or intubation.

2 Points: Good. Jaw and vocal cords well relaxed, slight cough upon laryngoscopy and/or intubation.

3 Points: Poor. Jaw not well relaxed, vocal cords slightly adducted, cough or movement upon laryngoscopy and/or intubation.

4 Points: Impossible. Jaw and/or vocal cords tightly closed.